Enantioselective Total Synthesis of (−)-Taxol

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Abstract: Enantioselective total synthesis of taxol has been accomplished. Coupling reaction of the optically pure A-ring hydroxy aldehyde with the aromatic C-ring fragment followed by Lewis acid mediated eight-membered B-ring cyclization gave the desired ABC endo-tricarbocycle. The C-ring moiety of this product was reduced under Birch conditions to the cyclohexadiene derivative, which was oxygenated by singlet oxygen from the convex β-face to give the C4β,C7β-diol stereoselectively. For introduction of the C19-methyl, the cyclopropyl ketone was prepared via cyclopropanation of the C-ring allylic alcohol or conjugate addition of a cyano group to the C-ring enone. Reductive cleavage of the cyclopropane ring followed by isomerization of the resulting enol to the corresponding ketone gave the crucial synthetic intermediate containing the C19-methyl group. Regioselective transformation of three hydroxyl groups of this intermediate, conversion of the C4-carbonyl group to the allyl chloride, and introduction of the C10-oxygen functionality afforded a precursor for D-ring construction. Dihydroxylation of the allyl chloride moiety followed by basic treatment of the resulting diol gave a fully functionalized taxol skeleton. Functional group manipulation of this product including attachment of the C13 side chain provided (−)-taxol.

Introduction

The taxane diterpenes[1] (Figure 1) isolated from several yew trees have a common tricarbocyclic structure containing an sp^2 carbon on their bridgehead C11-sites.[2] Such a unique structural feature as well as many oxygenated asymmetric centers has made them extremely challenging synthetic targets. Among various taxanes, taxol[3] (**1**) isolated from extracts of the bark of *Taxus brevifolia* was shown to act as a promoter of microtubule assembly[4] and has been well-documented to exhibit promising activity against a number of human cancers.[5] Further, some members of its family such as taxinine and taxuspines were also reported to exhibit multidrug resistance reversing activity.[6]

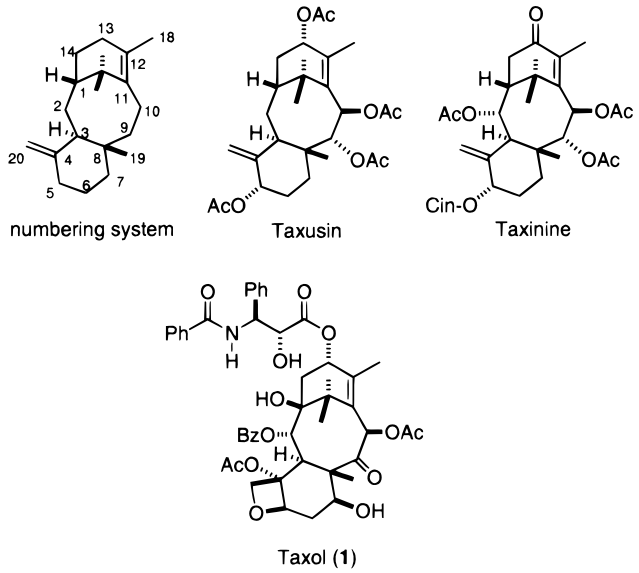

Figure 1.

These features have prompted synthetic studies to lead to successful total syntheses.[7,8,10]

The major problems in taxane synthesis seem to be focused on the following two aspects: (1) construction of a highly distorted ABC-tricarbocyclic structure, and (2) stereocontrol of many asymmetric centers. To solve the first problem, we developed a useful methodology which allowed construction of the taxane ABC-tricarbocycle from AC-fragment **A** via connection between the C9 and C10 atoms.[9] Although this aldol-like C−C bond formation is assumed to produce several stereoisomers, the cyclized product was usually obtained as a

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(1) (a) Lythgoe, G. *The Alkaloids*; R. H. F., Ed.; Academic Press: New York, 1968; Vol. 10, p 597. (b) Miller, R. W. *J. Nat. Prod.* **1980**, *43*, 425. (c) Kingston, D. G. I.; Molinero, A. A.; Rimoldo, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1.

(2) The taxane numbering system, as illustrated in Figure 1, is used throughout.

(3) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(4) Horwitz, S. B.; Fant, J.; Schiff, P. B. *Nature* **1979**, *277*, 665. Schiff, P. B.; Horwitz, S. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1561. Schiff, P. B.; Manfredi, J. J.; Horwitz, S. B. *Pharmacol. Ther.* **1984**, *25*, 83.

(5) For reviews, see: (a) *Taxol: Science and Applications*; Suffness, M., Ed.; CRC: Boca Raton, FL, 1995. (b) *Taxane Anticancer Agents: Basic Science and Current Status*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (c) Runowicz, C. D.; Wiernik, P. H.; Einzig, A. I.; Goldberg, G. L.; Horwitz, S. B. *Cancer* **1993**, *71*, 1591. (d) Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol.* **1992**, *19*, 646.

(6) (a) Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401. (b) Morita, H.; Wei, L.; Gouda, A.; Takeya, K.; Itokawa, H.; Fukaya, H.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 4621.

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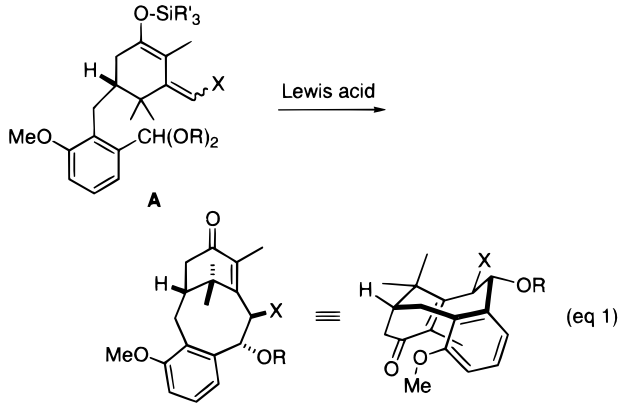
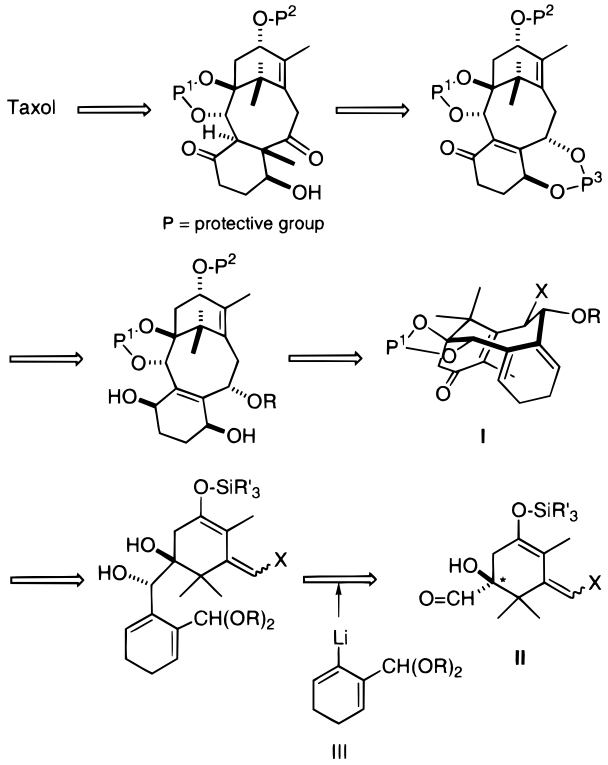
single endo conformer containing C9α,C10β substituents irrespective of the geometry of the dienol silyl ether moiety (eq 1).



We have previously described a synthesis of the relatively simple taxusin, where the present methodology was efficiently applicable for construction of the taxusin ABC-tricarbocycle. Subsequent functional group manipulations completed the total synthesis of (+)-taxusin.[8b]

Considering a much more complex and challenging structure as well as important biological activities, total syntheses of natural taxol and its structural analogues are expected to bring much greater advances both in synthetic organic chemistry and in the clinical field. We explored an efficient pathway to the more challenging (−)-taxol. This paper describes the full details of our synthesis of (−)-taxol.[10]

Scheme 1. Retrosynthetic Analysis



Synthetic Plan

Our program for taxol synthesis was based on the initial construction of endo tricarbocyclic intermediate **I** (Scheme 1) with correct stereochemistry at C1 and C2, followed by appropriate functional group manipulations on the B- and C-rings. The structural features of **I** favor an introduction of the C19-methyl from the convex face of the C-ring. Our choice of a C-ring fragment was rather crucial at this stage, but among several candidates, we preferred a cyclohexadiene derivative since it was expected that the use of the diene C-ring fragment **III** would permit an eventual installation of C4 and C7 oxygen functionalities from the convex β-face of **I**. We also envisioned that the present approach would lead to an enantioselective synthesis of taxol by using the aldehyde **II** with a chiral center corresponding to the C1 site. Thus, a chelation-controlled coupling of the optically active α-hydroxy aldehyde[11] with a C-ring fragment would confirm the stereochemical outcome at the C1 and C2 sites, and a subsequent B-ring cyclization would lead to the diastereoselective formation of the key intermediate **I** for taxol. On the basis of the retrosynthetic analysis shown in Scheme 1, we executed an enantioselective total synthesis of (−)-taxol.

Enantioselective Preparation of the A-Ring Fragment

The optically active A-ring fragment **8** was prepared as follows (Schemes 2 and 3).[11] Addition of lithiated propargyl ether to propionaldehyde followed by Lindlar reduction and

(7) Taxol synthesis: (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (b) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (c) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757. (e) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Jpn. Acad. Ser. B* **1997**, *73*, 95. Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 1. Shiina, I.; Saitoh, K.; Fréchard-Ortuno, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 3. Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121.

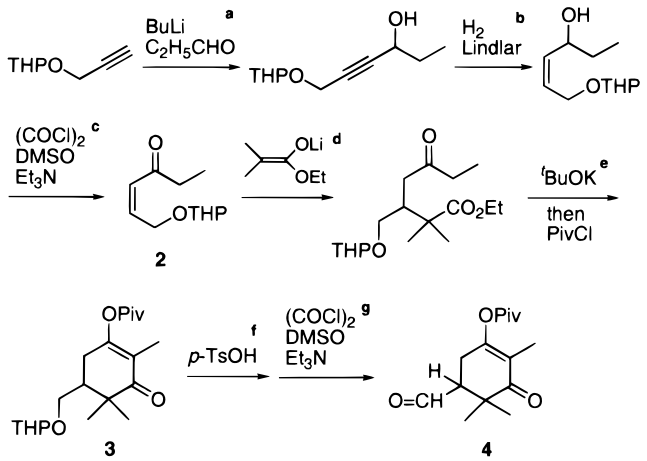
(8) Taxusin synthesis: (a) Holton, R. A.; Juo, R. R.; Kim, H.-B.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558. (b) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186. Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072. (c) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203. Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

(9) (a) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (b) Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. (c) Seto, M.; Morihira, K.; Katagiri, S.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Chem. Lett.* **1993**, 133. (d) Morihira, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345.

(10) For the preliminary communication, see: Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980.

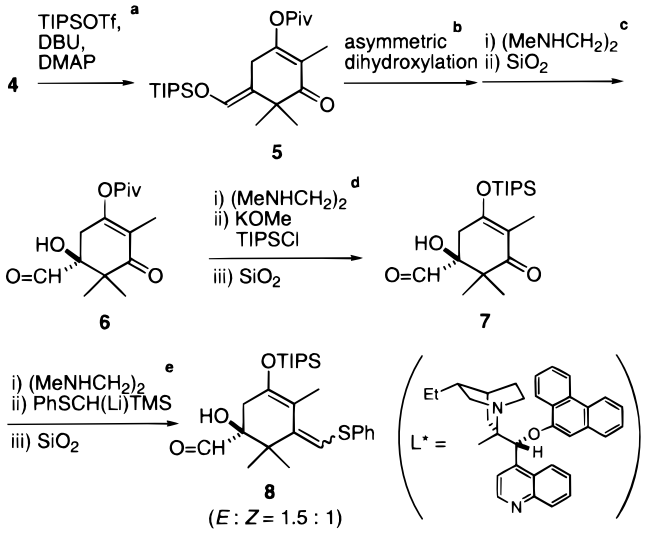
(11) (a) Nakamura, T.; Waizumi, N.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1994**, *35*, 7813. (b) Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165.

Scheme 2. Preparation of the A-Ring Fragment. 1[a]



[a] (a) THF, −78 to 0 °C, 3 h; (b) hexane, rt, 7 h; (c) CH_2Cl_2, −78 °C to rt, 10 h; (d) THF, − 78 °C, 0.5 h; 0 °C, 0.5 h; (e) Et_2O, 0 °C, 3 h; CH_2Cl_2, rt, overnight; (f) MeOH, rt, 3 h, 52% for six steps; (g) CH_2Cl_2, −78 to 0 °C, overnight, 92%.

Scheme 3. Preparation of the A-Ring Fragment. 2[a]



[a] (a) CH_2Cl_2, −78 °C to rt, 4 h, 71%; (b) $K_2OsO_2(OH)_4$, $K_2Fe(CN)_6$, K_2CO_3, DHQ-PHN, *t*-BuOH, 0 °C, 11 h, 98%; (c) benzene, reflux, 0.5 h, 98%; (d) (i) benzene, reflux, 0.5 h; (ii) THF, −23 °C, 6 h, 62%; (e) (i) benzene, reflux, 0.5 h; (ii) THF, 0 °C, 3 h, 64%.

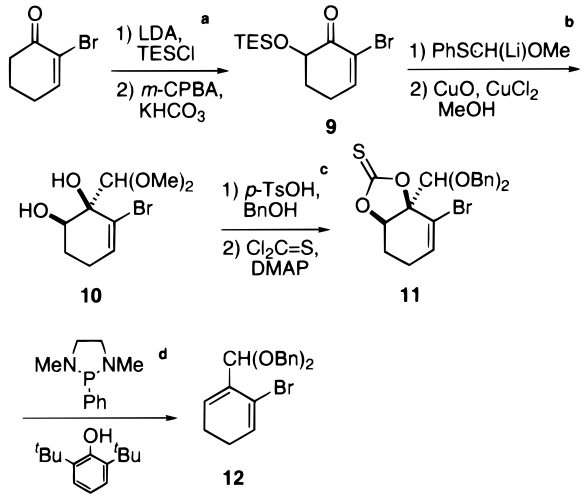
Swern oxidation gave enone **2**. Conjugate addition of isobutyric ester enolate to **2** took place smoothly to produce the keto ester shown, which underwent Claisen-like cyclization on exposure to ^{t}BuOK. The resulting β-diketone was then converted to pivaloate **3**. Removal of the THP protecting group followed by Swern oxidation afforded aldehyde **4** in ca. 50% overall yield from propargylic ether. The above transformation could be performed on a molar scale without purification of the intermediates.

Conversion of **4** to enol silyl ether **5** was achieved as shown in Scheme 3. Owing to the geminal methyl groups, enol ether **5** was obtained as the *E*-isomer exclusively. The geometry of the double bond was determined by the observed NOE from the *gem*-dimethyl group to the olefinic proton. Application of Sharpless's asymmetric dihydroxylation[12] using DHQ-PHN as a chiral ligand to **5** produced α-hydroxy aldehyde **6** in good enantioselectivity (90% ee).[13] However, isolation of **6** from the basic media with good recovery was quite difficult due to a facile formation of dimeric isomers; hence, the crude mixture including a monomer and dimers was treated with *N*,*N*′-dimethylethylenediamine in boiling benzene to convert **6** to its aminal. Purification of the resultant aminal by silica gel column chromatography was accompanied by removal of the protecting group to give pure hydroxy aldehyde **6** as a monomer. Recrystallization from benzene−hexane afforded the enantiomerically pure α-hydroxy aldehyde (>98% ee). The optical purity of **6** was determined by ^{1}H NMR analysis of the MTPA ester derived from the reduction of **6**, followed by acylation of the resulting alcohol. After protecting the aldehyde moiety as an aminal, the pivaloyl group was changed to a TIPS group in a one-pot operation, and elution through a silica gel column again allowed removal of the aminal moiety to give aldehyde **7**. According to a similar operation, Peterson olefination of **7** afforded dienol silyl ether **8** as a mixture of geometrical isomers on the vinyl sulfide moiety (*E*:*Z* = ca. 1.5:1).[14] Although **8** could be prepared from **6** without removal of the aminal moiety as in the conversion of **6** to **7**, the above procedure gave much higher reproducibility.

Construction of the ABC Tricarbocycle

(a) Use of Cyclohexadiene Derivative as a C-Ring Fragment. As the first candidate for a C-ring fragment, 2-bromo-1,3-cyclohexadiene derivative **12** was chosen and prepared as shown in Scheme 4. Thus, introduction of a triethylsiloxy group onto the 6-position of 2-bromocyclohexenone was performed by oxidation of the corresponding enol silyl ether with *m*-CPBA. Addition of PhSCH(Li)OMe[15] to the carbonyl group of **9** occurred from the opposite side of the OTES group to give the *cis*-diol derivative predominantly along with a small amount

Scheme 4. Preparation of the C-Ring Fragment[a]



[a] (a) (1) THF, −78 °C, 0.5 h; (2) CH_2Cl_2, 0 °C, 0.5 h, 96% in two steps; (b) (1) THF, −78 °C, 2 h; (2) THF−MeOH, reflux, 4 h, *cis*-isomer 54%, *trans*-isomer 7% from **9**; (c) (1) benzene, reflux, 6 h; (2) CH_2Cl_2, 0 °C to rt, 0.5 h, 64% from **10**; (d) THF, rt, 2 days, 82%.

(12) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(13) Absolute stereochemistry was determined on the basis of the X-ray crystallographic analysis of the derivative of **7**. See also: Takenaka, Y.; Kubo, S.; Ohashi, Y.; Nakamura, T.; Waizumi, N.; Horiguchi, Y.; Kuwajima, I. *Acta Crystallogr.* **1994**, *C50*, 1820.

(14) We initially planned benzyloxymethylenation of the carbonyl group of **7** on the basis of the high efficacy realized in taxusin synthesis;[8b] however, the reaction of **7** with benzyloxymethyllithium did not give the desired adduct in acceptable yield.

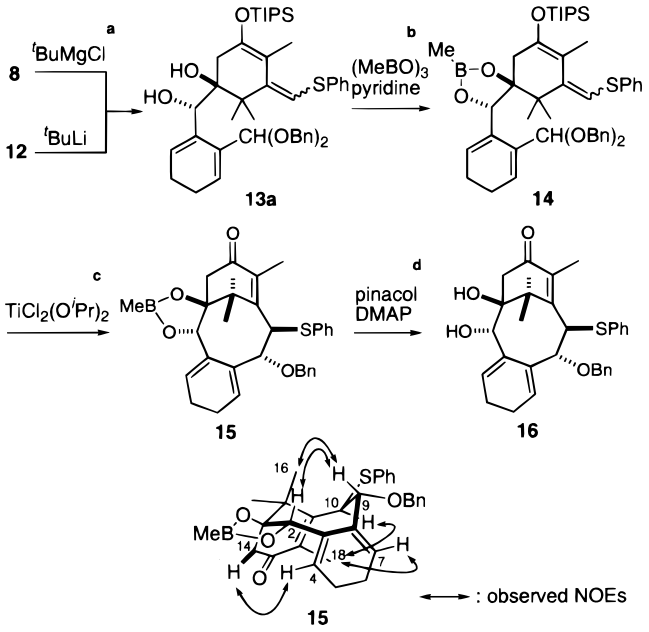
(15) Mandai, T.; Hara, K.; Nakajima, M.; Otera, J. *Tetrahedron Lett.* **1983**, *24*, 4993.

of the corresponding *trans*-isomer. The *O,S*-acetal moiety was changed to a dibenzyl acetal via dimethyl acetal **10**. Conversion of the vicinal diol moiety to the corresponding thionocarbonate **11**, followed by heating with diazaphospholidine according to Corey et al.,[16] afforded cyclohexadiene **12**. This compound should be kept in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) under a nitrogen atmosphere at low temperature; otherwise **12** easily decomposes to form unidentified white solids probably due to radical polymerization.

The chelation-controlled addition of the vinyllithium reagent derived from **12** to **8** was performed in the presence of Mg(II) ion to give the corresponding coupling product **13a** as a single isomer (Scheme 5). The stereochemistry at the C2 site was determined on the basis of the observed NOEs of cyclized product **15** at the later stage. The ^{1}H NMR spectrum of the resulting adduct was highly broadened. This suggested that **13a** consisted of atropisomers arising from the rotational barrier on the C2−C3 bond, which were interconverting at room temperature. This phenomenon was also found in a similar substrate having an aromatic C-ring.[17] On the contrary, connection of the C1,2-diol moiety as the boronic ester gave **14** which showed sharp signals in the ^{1}H NMR spectrum. Preliminary studies suggested that the boronate derivative consisted of the desired (P)-isomer where an acetal moiety is closely situated to the terminal of the dienol ether to favor the eight-membered B-ring cyclization.[17]

Among several Lewis acid examined, $TiCl_2(O^iPr)_2$ proved to be the most efficient to induce the B-ring cyclization in this case. The stereochemistry of cyclized product **15**, namely the conformation of the B-ring and configuration of the C9 and C10 sites as well as the C2 hydroxyl group, was determined on the basis of the observed NOEs shown below.[18] For subsequent removal of the boron protecting group, the use of pinacol with DMAP efficiently produced the corresponding diol **16**.

Scheme 5. Construction of the Tricarbocycle[a]

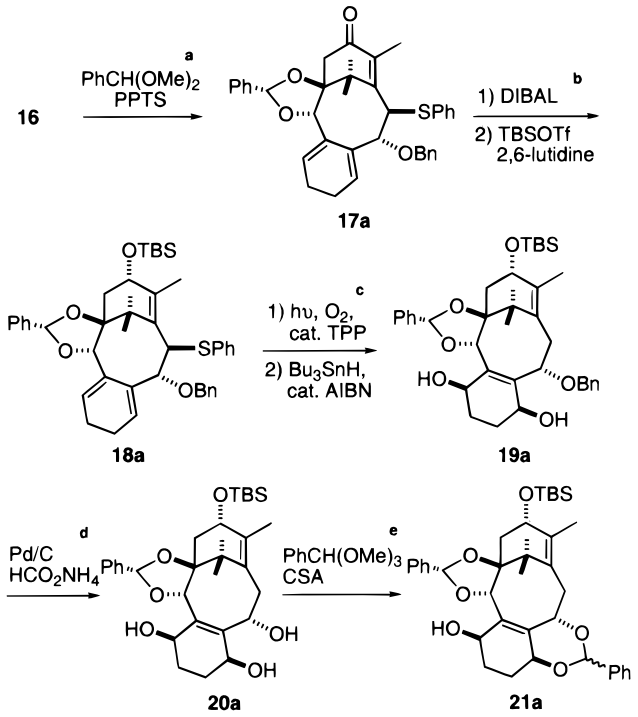


[a] (a) THF, −78 °C, 0.5 h (preparation of magnesium alkoxide), then lithiated **12**, −78 °C, 1 h, 68%; (b) benzene, rt, 0.5 h, 77%; (c) CH_2Cl_2, −78 °C to 0 °C, 1.5 h; (d) benzene, rt, 59% from **14** in two steps.

(16) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979.

(17) Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 584.

Scheme 6[a]



[a] (a) Benzene, reflux 1 h; (b) (1) CH_2Cl_2, −78 °C, 1 h; (2) CH_2Cl_2, −23 °C, 1 h, 80% from **16**; (c) (1) CH_2Cl_2, rt, 4 h; (2) benzene, reflux, 4 h, 85% from **18a**; (d) EtOH, rt, 1 h; (e) CH_2Cl_2, 0 °C, 2.5 h, 87%.

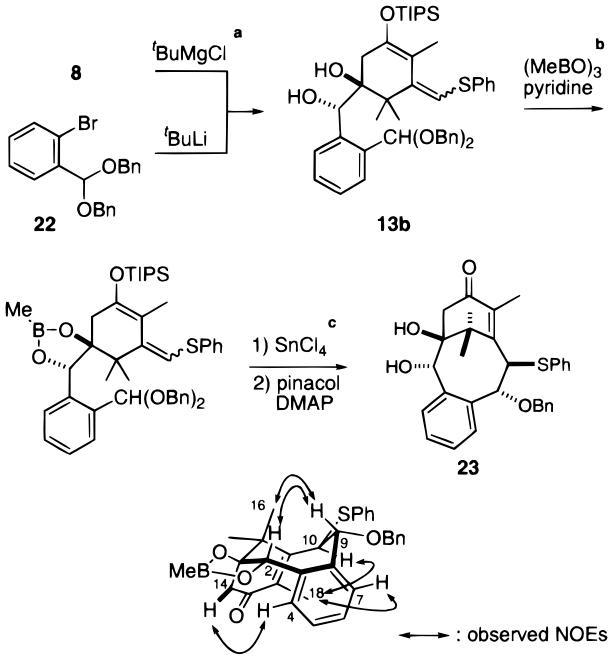
Protection of the 1,2-diol moiety with a benzylidene group produced α-isomer **17a** exclusively, and reduction of the C13 keto group followed by silylation with TBSOTf afforded **18a** (Scheme 6). Singlet oxygen oxygenation of the 1,3-diene moiety took place selectively from the *β*-face of the C-ring, and subsequent treatment with Bu_3SnH and a catalytic amount of AIBN induced both the peroxide bond cleavage and removal of the phenylthio group to yield **19a**. Removal of the benzyl group, followed by protection of the C7,9-diol, afforded **21a** as a mixture of two diastereomers (α:*β* = ca. 1:1).

(b) Use of an Aromatic C-Ring Fragment. A drawback in the use of the C-ring fragment **12** was lability of the 1,3-diene moiety which appeared to undergo facile polymerization to form a considerable amount of waxy substances under several reaction conditions or during workup procedures. Although such polymerization could be prevented by performing operations in the presence of a small amount of BHT, development of a more convenient route was desirable, especially for large-scale operations. We conceived a new route by way of a C9-keto tricarbocycle with a readily available aromatic C-ring. Thus, 2-bromobenzaldehyde dibenzylacetal **22** was used as a C-ring fragment. Successive operations of coupling between the A- and C-rings, protection of the 1,2-diol moiety, and $SnCl_4$-induced eight-membered B-ring cyclization gave the corresponding tricarbocycle **23** after removal of the boron protecting group. The stereochemistry of **23** was the same as that of **15** (Scheme 7).

From compound **23**, a Birch reduction precursor was prepared (Scheme 8). Reduction of the C13-carbonyl group followed by protection of the C2- and C13-hydroxyl groups with TBSOTf

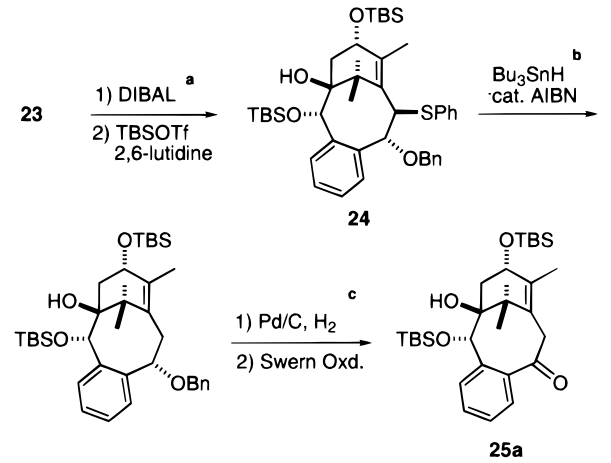
(18) Although the cyclization precursor **14** was a mixture of geometrical isomers on the vinyl sulfide moiety (*E*:*Z* = ca. 1.5:1), *E*/*Z* isomerization took place under the cyclization reaction conditions and the thermodynamically most stable tricarbocycle **15** was obtained as a major product. For the proposed mechanisms of the *E*/*Z* isomerization, see ref 9d.

Scheme 7. Construction of the Tricarbocycle (Aromatic Route)[a]



[a] (a) THF, −78 °C, 0.5 h (preparation of magnesium alkoxide), then lithiated **22**, −78 °C, 1 h, 74%; (b) benzene, rt, 12 h, 90%; (c) (1) CH_2Cl_2, −78 to −45 °C, 1.5 h; (2) benzene, rt, 40 h, 76% in two steps.

Scheme 8. Preparation of Birch Reduction Precursor[a]

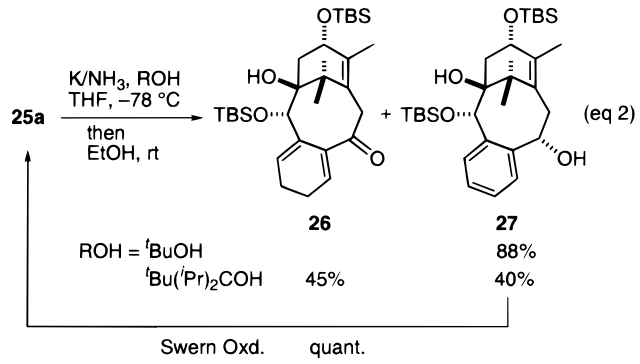


[a] (a) (1) CH_2Cl_2, −78 °C, 1.5 h; (2) CH_2Cl_2, −78 °C, 2 h, 82% from **23**; (b) benzene, reflux, 2 h, quantitative; (c) (1) EtOH, rt, 2 h, 91%; (2) CH_2Cl_2, −78 °C to rt, 0.5 h, quantitative.

produced **24**. Removal of the phenylthio and benzyl groups followed by Swern oxidation afforded the desired aryl ketone **25a**.

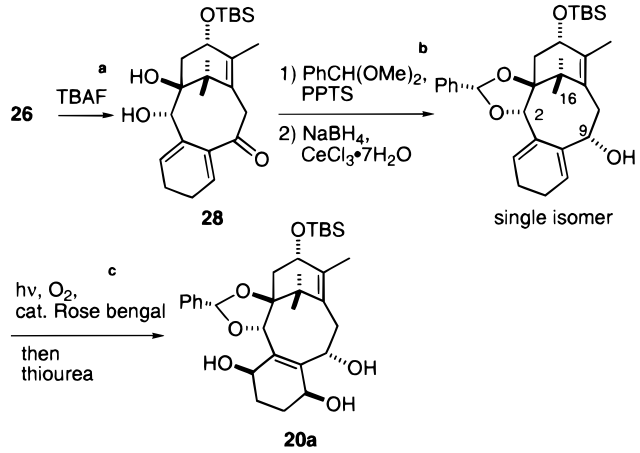
Several attempts at Birch reduction of aryl ketone **25a** disclosed a rather unexpected result. Reduction in the presence of *tert*-butyl alcohol as a proton source failed to reduce the aromatic ring but produced the corresponding benzyl alcohol **27** exclusively (eq 2). This unusual phenomenon may be attributed to the unique structural feature of substrate **25a** which allows **25a** to exhibit behavior different from that of the usual benzoyl group: semiempirical MO calculation of **25a** using the PM3 Hamiltonian[19] revealed that the benzene ring is situated almost perpendicular to the C9 carbonyl group.

(19) SPARTAN (ver. 4.1.1) was used for PM3 calculations.



With the expectation that use of a sterically hindered alcohol as a proton source would allow for preferential protonation on the sterically less-demanding aromatic ring rather than at the C9 site, we examined Birch reduction in the presence of various highly substituted alcohols, and we were pleased to find that the use of 2,2,4-trimethyl-3-isopropyl-3-pentanol led to a satisfactory result. Thus, reduction of **25a** (K/liquid NH_3, THF, −78 °C, 2 h) and successive in situ treatment with EtOH (rt, 2 h) gave an almost 1:1 mixture of conjugated diene **26** and benzyl alcohol **27**. Since the latter could be recovered as starting material **25a** via Swern oxidation in excellent yield, a total conversion is considered acceptable for synthetic purposes. Ketone **26** was converted to allylic alcohol **20a**, which was found to be identical to that obtained from the diene-type C-ring fragment shown in Schemes 5 and 6 (Scheme 9).

Scheme 9[a]

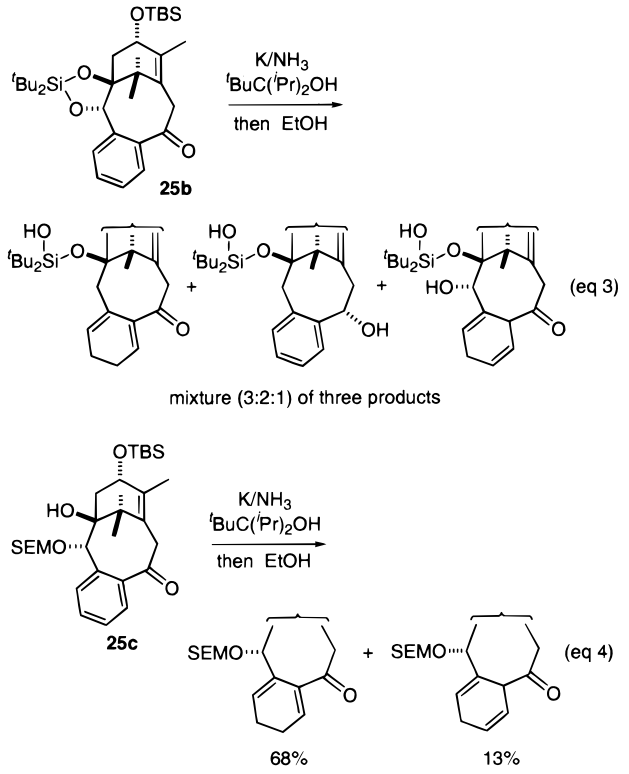


[a] (a) THF, 0 °C, 1 h, 98%; (b) (1) benzene, reflux, 1 h, 89%; (2) MeOH − THF, 0 °C, 1 h, quantitative; (c) CH_2Cl_2−MeOH, rt, 1 h; rt, 17 h, 74%.

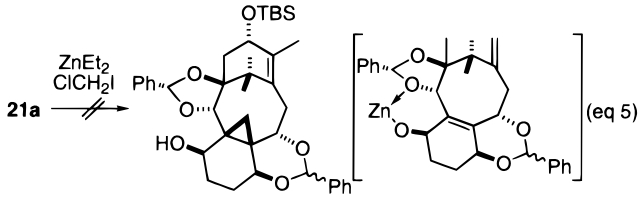
We also investigated the Birch reduction of derivatives of **25a** with various protecting groups on the C2-OH: reaction of the di-*tert*-butylsilylene derivative **25b** induced C2−O bond cleavage predominantly (eq 3). Use of the C2-*O*-SEM substrate **25c** gave a much more satisfactory result (eq 4), but we encountered much difficulty in removing the SEM group at a later stage; the SEM group was thus deemed to be unsuitable for the present purpose.

Introduction of C19 Methyl Group

(a) Route via Cyclopropanation. For introduction of the C19-methyl, we adopted a strategy similar to that of our taxusin synthesis involving a hydroxyl group-directed cyclopropanation on the $\Delta^{3,8}$-double bond, followed by ring cleavage of the



cyclopropyl ketone. By using $Et_2Zn/ClCH_2I$[20] or Et_2Zn/ICH_2I, we attempted to transfer a methylene group on **21a**, but the $\Delta^{3,8}$-double bond of **21a** was found to be very unreactive, giving back the starting materials irrespective of extensive examinations (eq 5).

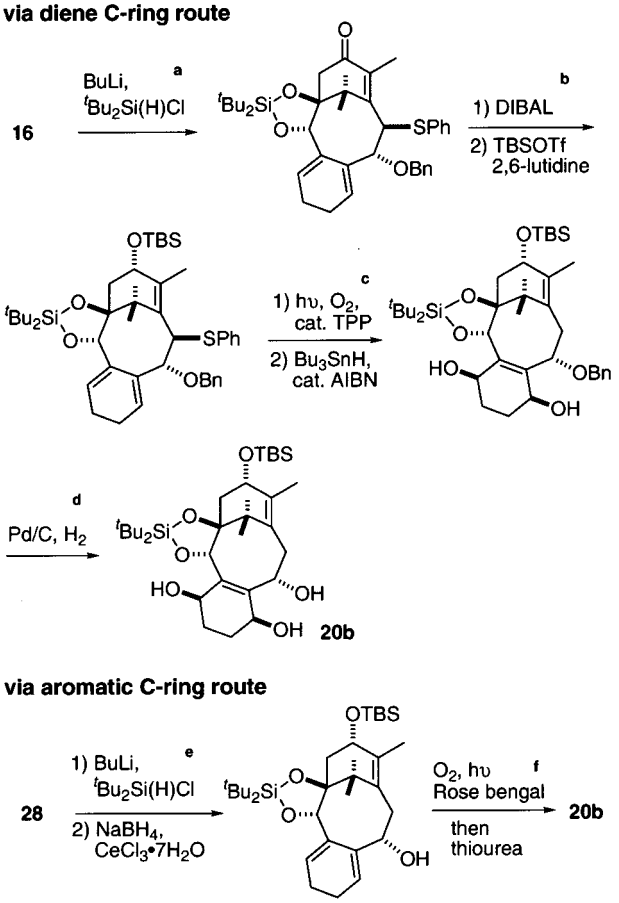


We assumed that the failure of **21a** to undergo cyclopropanation was due to the strong coordination of the C2 oxygen to zinc on the C4-OH group where a methylene group on the zinc has little chance to engage the $\Delta^{3,8}$-double bond. To circumvent this problem, we explored di-*tert*-butylsilylene as a protecting group to make the C2 oxygen much less basic. Thus, ketone **16** was treated successively with BuLi and $^tBu_2Si(H)Cl$ at low temperature. On warming, hydrogen evolved to give the dioxasilapentane.[21] A successive application of procedures similar to those described in Scheme 6 afforded triol **20b**, which was also prepared via the aromatic C-ring route as shown in Scheme 10.

Then the C7,9-diol moiety of **20b** was protected with various protecting groups and cyclopropanation of the $\Delta^{3,8}$-bond was investigated. Although the substrates with a carbonate or an acetonide group on the C7,9-diol did not react with the zinc carbenoid reagent, the benzylidene-protected substrate was found to undergo cyclopropanation (Scheme 11). Of the two diastereomers of **21b** (α:β = ca. 1:4), the major β-isomer underwent the expected methylenation on treatment with a zinc reagent prepared by $ZnEt_2$ and $ClCH_2I$ in toluene to produce **29**, whereas

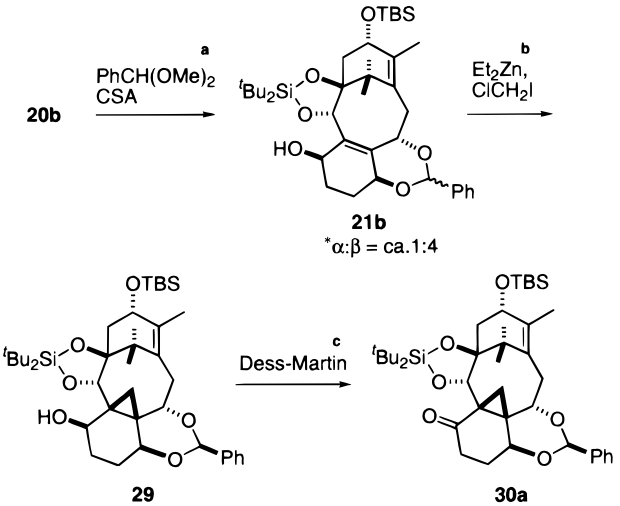
(20) Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974.
(21) Tanino, K.; Shimizu, T.; Kuwahara, M.; Kuwajima, I. *J. Org. Chem.* **1998**, *63*, 2422.

Scheme 10. Preparation of the Triol **20b**[a]



[a] (a) THF, −78 to 0 °C, 1.5 h; (b) (1) CH_2Cl_2, −78 °C, 1 h; (2) CH_2Cl_2, −23 °C, 0.5 h, 62% from **16** in three steps; (c) (1) CH_2Cl_2, rt, 7 h; (2) benzene, reflux, 12 h, 80% in two steps; (d) EtOH, rt, 4.5 h; (e) (1) THF, −78 °C, 2 h, 67%; (2) MeOH, 0 °C, 0.2 h, 79%; (f) CH_2Cl_2, rt, 0.5 h, CH_2Cl_2−MeOH, rt, 0.5 h, 50%.

Scheme 11. Preparation of the Cyclopropyl Ketone **30a**[a]

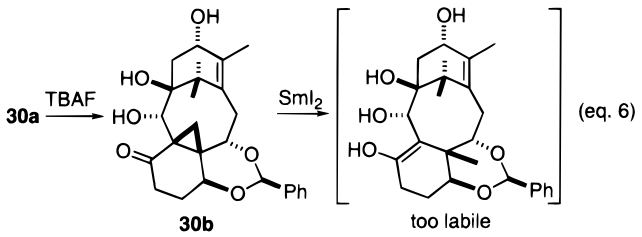


[a] (a) CH_2Cl_2, −23 °C, 12 h, 79%; (b) toluene, 0 °C, 0.5 h, 66%; (c) CH_2Cl_2, rt, 12 h, 77%.

the methylene transfer could not be effected with the α-isomer. NOE experiments of the α-isomer indicated that it contains the boat conformation of the 1,3-dioxolane ring where the benzylic hydrogen seems to prevent an approach of the reagent to the double bond. Dess−Martin oxidation of **29** afforded the corresponding cyclopropyl ketone **30a**.

During synthetic studies of taxusin, we discovered that the C13-OH plays a critical role in converting the enol produced by cyclopropane ring cleavage to the desired ketone. Conversion of a $\Delta^{3,4}$-enol bearing a protected C13-hydroxyl to a C3α-protonated ketone via intermolecular protonation is exceedingly difficult because the protonation to C3 must occur from a narrow space between the A- and C-rings. To overcome the difficulty encountered in our prior synthesis of taxusin, we achieved this enol/keto isomerization by exploiting the closely situated C13-OH for protonation on C3 from the α-face.[8b]

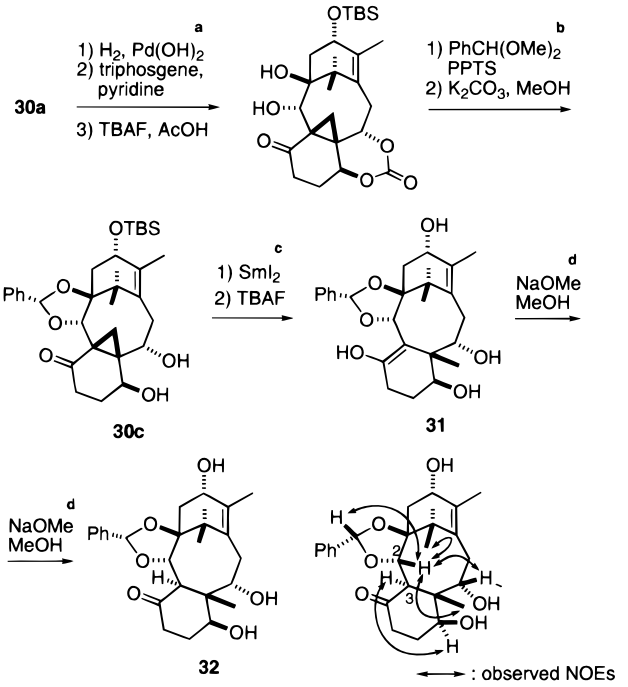
On the basis of this observation, we initially removed the C13- as well as C1,2-silicon protecting groups of **30a**, and the resulting triol **30b** was used for the ring cleavage. Under the influence of SmI_2, the cyclopropane ring cleavage took place readily, but the resulting enol was exceptionally unstable, and, in the presence of air, the enol quickly decomposed to form a complex mixture of unidentified products (eq 6).



Then we decided to examine the enol/keto isomerization by using the C1,2-diol-protected substrates. Several experiments revealed that the choice of the protecting group on the C1,2-diol and the C7,9-diol moieties was quite important to realize the isomerization of the enol to the corresponding ketone, and the following procedure was found to give a satisfactory result: replacing the C7,9-protecting group of **30a** with carbonate, followed by removal of the di-*tert*-butylsilylene group with TBAF, gave the diol. After protection of the C1,2-diol moiety with a benzylidene group (single isomer), treatment with methanolic K_2CO_3 yielded **30c**. On exposure to SmI_2−HMPA[22] in methanol, **30c** was smoothly converted to an enol stable enough for manipulation under various reaction conditions. Similar to the taxusin synthesis,[8b] the C13-protected enol did not isomerize to the ketone at all, and removal of the TBS group followed by basic treatment (NaOMe/MeOH) induced the isomerization to give an almost 1:1 equilibrium mixture[23] of **31** and the C3α-protonated ketone **32**. Finally, **32** was obtained in 65% yield by repeating twice this enol−keto isomerization procedure. The stereochemistry of the C3 site was determined by NOE experiments as well as by the coupling constant of the C3 proton (doublet, $J = 5.6$ Hz) (Scheme 12).

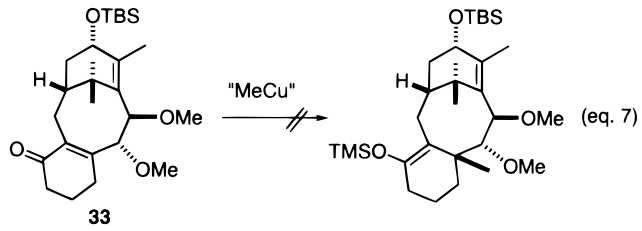
(b) Conjugate Addition Approach. Although starting from the tricarbocycle **16** we could prepare the important synthetic intetmediate **32** for taxol synthesis, the protecting groups of the C1,2- and C7,9-diols had to be exchanged frequently to promote the desired transformations as described in the above section. To improve this situation, we reinvestigated a route including a conjugate addition reaction for introduction of the C19-methyl group. During our study of taxusin synthesis, we experienced that introduction of a methyl group onto the C-ring enone via conjugate addition could not be effected with C9,10-dimethoxy-

Scheme 12. Reductive Cleavage of the Cyclopropyl Ketone[a]

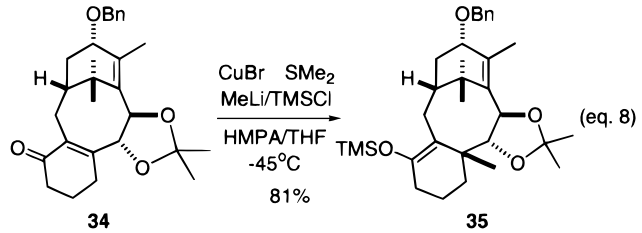


[a] (a) (1) EtOH, rt, 0.5 h, 84%; (2) CH_2Cl_2, −45 °C, 2 h; (3) THF, rt, 2.5 h, 95% in two steps; (b) (1) benzene, reflux, 1 h, 86%; (2) THF, rt, 1 h, quantitative; (c) (1) THF, rt, 5 h, quantitative; (2) THF−cat. BHT, rt, 3 h; (d) degassed MeOH-cat. BHT, rt, 2.5 days, 45% in two steps (ca 50% of **31** was recovered); 65% by repeating this isomerization procedure.

substituted **33**, even with the use of any type of methylcopper or manganese reagent (eq 7). A molecular modeling study



suggested that the C9-methoxy group might prevent the conjugate addition to the C-ring enone moiety due to a buttressing effect. Thus, we undertook an experiment using acetonide-protecting substrate **34**. Use of a combination of Me_2-CuLi/TMSCl[24] induced the desired addition reaction to afford methylated product **35** in good yield as the enol silyl ether (eq 8).



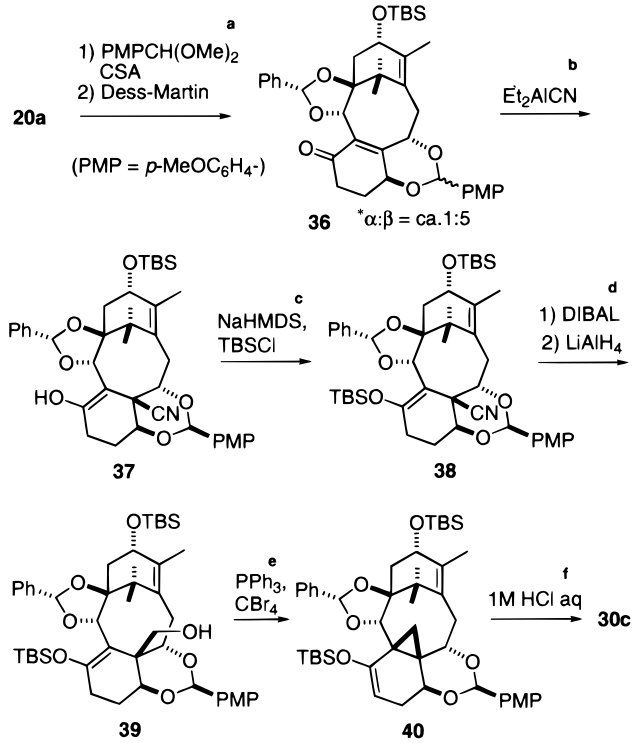
On the basis of these observations, we attempted to introduce the angular methyl group via conjugate addition to enone **36**, which was readily available from triol **20a** (Scheme 13). Various

(22) Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211.

(23) Isomerization of the enol containing benzylidene groups on the C1,2- and C7,9-diol moieties to the corresponding ketone did not proceed at all. Thus, the free C7,9-hydroxyl groups were indispensable to obtain the desired ketone.

(24) (a) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025. (b) Matsuzawa, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* **1989**, *45*, 349.

Scheme 13. Conjugate Addition Route[a]



[a] (a) (1) CH_2Cl_2, −23 °C, 1 h, 90%; (2) CH_2Cl_2, rt, 1 h, 95%; (b) toluene, rt, 6 h, 74%; (c) THF, 0 °C, 0.2 h, 88%; (d) (1) CH_2Cl_2, −78 °C, 0.2 h, 78%; (2) THF, −78 °C, 0.3 h, 95%; (e) benzene−pyridine, 50 °C, 0.5 h, 88%; (f) acetone, rt, 0.5 h, quantitative.

efforts to direct the introduction of a methyl group or its equivalent using copper reagents or stabilized carbanions were fruitless, probably due to a much larger steric congestion around the reaction site as compared with that of taxusin-type substrate **35**. Nevertheless, a cyano group could be introduced quite efficiently by treatment of **36** (α:β = ca. 1:5) with Et_2AlCN in toluene to give stable enol **37** in good yield.[25] Stereochemistries of the benzylidene and *p*-methoxybenzylidene moieties were determined by NOE experiments. The phenyl group of the benzylidene moiety was assigned the α-configuration on the basis of the NOE between the C2β-proton and the acetal methine proton. As for the *p*-methoxybenzylidene moiety, the NOEs between the acetal methine proton and the C7α as well as the C10α protons revealed the β-configuration of the *p*-methoxyphenyl group. Under the above reaction conditions, the stereochemistry of the *p*-methoxybenzylidene moiety was completely isomerized to the thermodynamically stable β-isomer; however, isomerization of the benzylidene stereocenter also occurred gradually to afford a small amount of the adduct containing the β-benzylidene. Enol **37**, the desired compound, was converted to the TBS enol ether **38**.

Next, the conversion of the cyano group of **38** to a methyl group was attempted by using a Wolff−Kishner-type reduction of the derived hydrazones or radical deoxygenation of the alcohol derivatives such as a xanthate, but all attempts failed. Furthermore, displacement of the hydroxyl group of **39** with a bromine atom only gave cyclopropane derivative **40**. Hence we changed our plan to the efficient preparation of cyclopropyl ketone **30c** as a common synthetic intermediate of the diene C-ring and the aromatic C-ring routes, and **40** was converted to **30c** by acid treatment quantitatively.

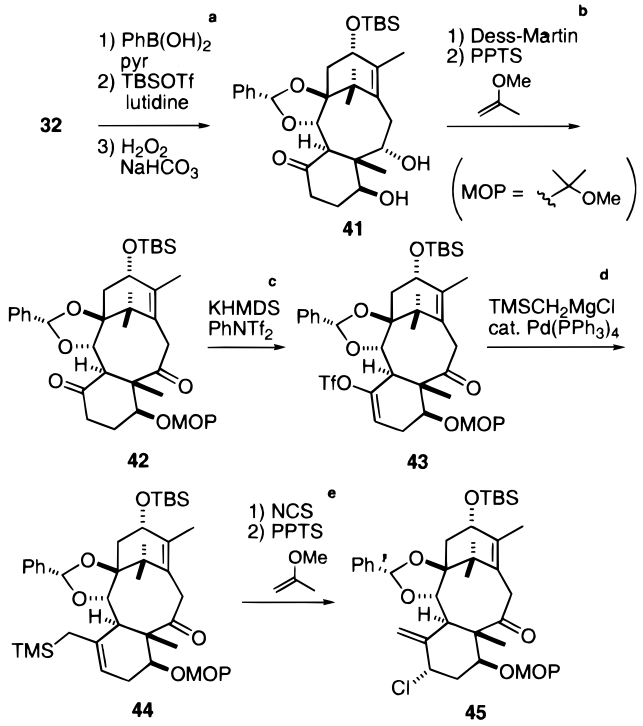
(25) Murai, A.; Tanimoto, N.; Sakamoto, N.; Masamune, T. *J. Am. Chem. Soc.* **1988**, *110*, 1985.

Thus, starting from enantiomerically pure α-hydroxy aldehyde **8**, the important synthetic intetmediate **32** could be prepared by using the aromatic C-ring fragment **22** and conjugate addition methodology without undergoing troublesome exchange of the protecting groups on the C1,2- and C7,9-diol moieties.

Functional Group Manipulation for (−)-Taxol Synthesis

With the intermediate **32** in hand, the first task we faced was how to discriminate three hydroxyl groups. The most desirable process was to protect the C7- and the C13-OH with different types of protecting groups and then to oxidize the C9-hydroxyl group to the corresponding ketone. Since the C7-OH seemed to be much less sterically demanding, selective protection of the C7-hydroxyl group by silylation (TBSOTf/2,6-lutidine) was initially examined, but silylation unexpectedly took place on the C9-OH selectively. Second, oxidation of the C9-OH was attempted, but Dess−Martin periodinane induced selective oxidation of the C13 hydroxyl group. By taking account of these features, we adopted the following strategy for protecting intermediate **32**. The C7,9-diol moiety was initially protected as a boronic ester ($PhB(OH)_2$/Py), and then the C13-OH was silylated with TBSOTf. After removal of the boron protecting group with hydrogen peroxide, selective oxidation of the C9-OH could be achieved with the Dess−Martin periodinane. The remaining C7-OH could then be protected as a 2-methoxy-2-propyl ether (MOP),[26] giving **42** in an appropriately differentiated form.

Scheme 14[a]

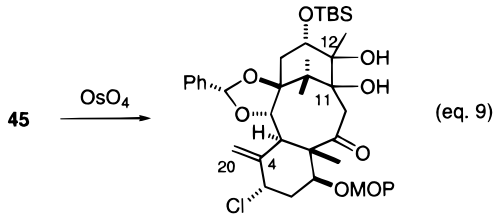


[a] (a) (1) CH_2Cl_2, rt, 0.25 h; (2) CH_2Cl_2, −45 °C, 12 h; (e) H_2O−AcOEt, rt, 1 h, 70% from **32** in three steps; (b) (1) CH_2Cl_2, rt, 1 h, 92%; (2) CH_2Cl_2, rt, 5 min, 97%; (c) THF, −78 °C, 1 h, 89%; (d) Et_2O, rt, 1 h, 91%; (e) (1) MeOH, rt, 10 h, 88%; (2) CH_2Cl_2, rt, 3 min, 89%.

(26) We initially chose a TES group as a protecting group on the C7-OH. However, in the case of introduction of a C10 functionality, migration of the TES group to a $\Delta^{9,10}$ enolate oxygen occurred to give an enol silyl ether. Protection with Bn or BOM groups also failed to afford a C7-epimerized alcohol under basic reaction conditions.

The next problem was to introduce the methylene group on the C4 site. We had already found Wittig reactions to be inefficient in our taxusin synthesis; therefore we decided to explore a more efficient methodology which may also serve to introduce a C5 functionality for installation of the D-ring at a later stage. To this end, we examined a selective conversion of **42** to **44** containing an appropriate allylsilane functionality via enol triflate **43**. Although **42** contains two ketone functions, the difference in steric circumstances allowed us to selectively generate a $\Delta^{4,5}$-enolate by treatment with KHMDS and quenching with Tf_2NPh to give **43** in good yield. Gratifyingly, the reaction of **43** with the Grignard reagent shown in Scheme 14 in the presence of a catalytic amount of $Pd(Ph_3P)_4$ afforded **44** in good yield.[27] Treatment of **44** with NCS in MeOH[28] gave the corresponding C5α-chloride **45**.

For construction of the D-ring, introduction of a diol moiety on the $\Delta^{4,20}$-double bond of **45** was next examined, but OsO_4 oxidation unexpectedly took place at the $\Delta^{11,12}$-double bond on the A-ring, yielding a C11,12-diol exclusively (eq 9).



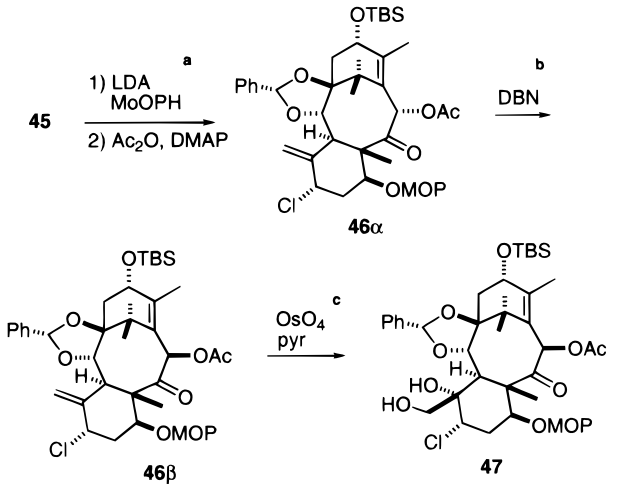
(eq. 9)

To increase steric congestion around the A-ring to effect selective dihydroxylation on the exomethylene moiety, we decided to introduce a C10 functional group initially. Functionalization of the C10 site could be performed by generation of the $\Delta^{9,10}$-enolate with LDA, followed by oxidation with MoO_5·pyr·HMPA (MoOPH),[29] giving the C10α-alcohol selectively. Although the stereochemical result was opposite from the natural form, inversion of the C10α-oxygen functionality to the thermodynamically more favored C10*β* configuration was achieved by treatment with a base. Among the several attempts examined, the following procedure gave the most satisfactory result. Thus, acetylation of the C10-hydroxyl group (Ac_2O/DMAP) gave **46**α which, on heating with DBN, induced clean isomerization to afford the desired C10*β*-acetate **46***β* (Scheme 15).

On applying OsO_4 oxidation to **46**α and **46***β*, the former still gave the corresponding C11,12-diol exclusively, whereas in the reaction with the latter, dihydroxylation took place selectively on the $\Delta^{4,20}$-site from the α-face to afford the desired **47** in good yield.

Such a difference may be due to the unique structural features of these tricarbocycles; NOE experiments as well as semiempirical MO calculations[19] of the C10α-acetate **46**α indicated that it contains the B- and C-rings as chair-chair and boat conformations, respectively. In such a structure, both the upper and lower sites of the $\Delta^{4,20}$-double bond suffer from severe steric hindrance, and dihydroxylation should occur on the sterically less demanding A-ring double bond. On the other hand, NMR experiments on the C10*β*-acetate **46***β* revealed the conformer containing the chair-boat B-ring and the chair form C-ring, in which the α-face of the exomethylene was the least hindered site for dihydroxylation (Figure 2).

Scheme 15. Dihydroxylation of the C-Ring[a]



[a] (a) (1) THF, −23 °C, 0.5 h, 80%; (2) CH_2Cl_2, rt, 0.5 h, 92%; (b) toluene, reflux, 10 h, 68% at 92% conversion; (c) Et_2O, rt, 12 h, 86%.

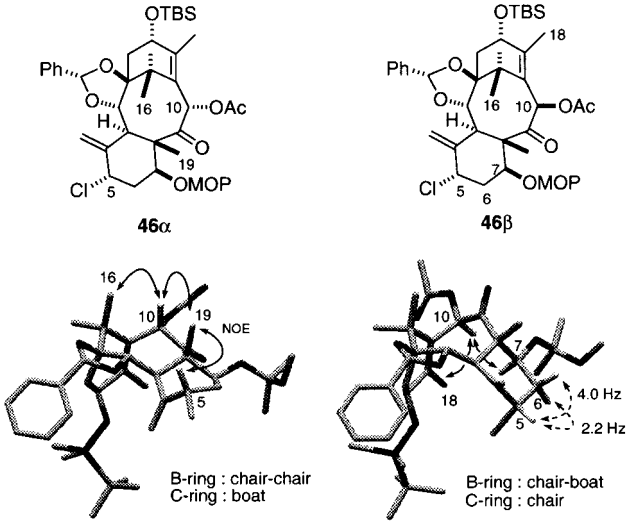


Figure 2. Conformation of C10α- and C10*β*-Acetates.

Heating **47** with DBU in toluene cleanly induced the oxetane ring closure to form the ABCD tetracyclic ring system **48** (Scheme 16). Then, we examined acetylation of the C4α-OH of **48**, but the reaction could not be effected under the usual conditions (Ac_2O or AcCl/Et_3N−DMAP). Even on using a combination of methyllithium and acetic anhydride, acetylation took place very sluggishly to yield the desired product in only ca. 30% yield. Considering that the phenyl group might prevent the acetylation of the C4α-OH, a sequence of replacement of the benzylidene group with the sterically less-demanding carbonate was undertaken.

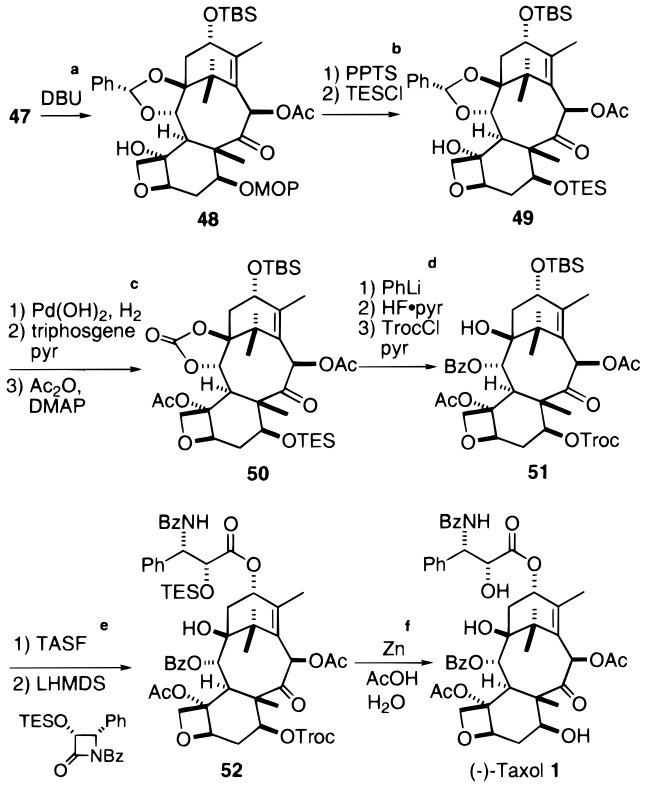
Since the MOP protecting group was also cleaved under the reaction conditions for removal of the benzylidene group (H_2/$Pd(OH)_2$), the MOP group was initially replaced by a TES group and then the C1,2-diol protecting group was converted from the benzylidene to the carbonate. The resulting carbonate cleanly underwent acetylation at the C4α-OH to afford **50**, and then the carbonate group was converted to the C2-benzoyloxy group by using known methodology,[7a,b,30] giving the C7,13-protected baccatin III. The TES group on the C7-OH was replaced by a Troc group and the TBS group was removed by treatment with

(27) This cross-coupling reaction was highly sensitive toward the ligands on palladium, and the use of triphenylphosphine was indispensable in obtaining the coupling product.

(28) The use of methanol as solvent was essential to obtain the allyl chloride in good yield. In the reaction of CH_2Cl_2, a vinylsilane was obtained as a major product.

(29) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

Scheme 16. Completion of the Total Synthesis of Taxol[a]



[a] (a) Toluene, reflux, 4 h, 86%; (b) (1) MeOH, rt, 0.5 h; (2) DMF, rt, 5 h, 97% from **48** in two steps; (c) (1) EtOH, rt, 1 h, 97%; (2) CH_2Cl_2, −78 to 0 °C, 1 h, 94%; (3) CH_2Cl_2, rt, 6 h, 66%; (d) (1) THF, −78 °C, 83%; (2) THF, rt, 2 h, 88%; (3) CH_2Cl_2, rt, 3 h, 94%; (e) (1) THF, rt, 2 days, 80%; (2) THF, −78 to 0 °C, 0.5 h, 77% at 90% conversion; (f) AcOH−H_2O, rt, 16 h, 84%.

TASF.[7a,31] Finally, acylation of the C13-OH by the β-lactam method[7a,32] followed by removal of the C7- and C2′-protecting groups completed our enantioselective total synthesis of (−)-taxol.

Conclusion

The total synthesis of natural (−)-taxol has been achieved. The most rewarding aspects are (1) an initial introduction of an asymmetric center on C1 which has allowed for control of all of the other asymmetric sites at later stages, (2) use of a simple C-ring fragment such as bromobenzaldehyde, and (3) a facile construction of the endo tricarbocycle, making it easy to introduce requisite functionalities stereoselectively.

Introduction of the angular methyl presented a synthetic problem. For cyclopropanation of the $\Delta^{3,8}$-double bond and the following cleavage of the cyclopropyl ketone **30c**, we had to exchange the protecting groups often, making this synthetic route rather lengthy. However, this problem could be overcome by using the alternative conjugate addition approach.

From the unique ABC tricarbocyclic structures, several interesting transformations were achieved: Birch reduction of a highly distorted aryl ketone function, and isomerization of the enol **31** to the ketone **32**.

Total synthesis is always accompanied by the formation of several artificial compounds, and we could produce several substrates with taxane-like carbon skeletons; among these, new useful drugs of stronger bioactivities might be produced.[33]

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Supporting Information Available: Spectroscopic data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Since the removal of the two silyl groups on **50** with TASF caused partial epimerization at the C7 stereocenter, the TES group on the C7-OH was exchanged to a Troc group.

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